Clinical outcomes in COVID-19 patients with pre-existing myasthenia gravis: A systematic analysis of reported cases

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ABSTRACT

INTRODUCTION: Myasthenia gravis (MG) presents an additional challenge in managing COVID-19 as outcomes potentially depend on prior disease control and treatment. Yet the role of pre-existing MG in COVID-19 outcomes has not been established.

METHODS: We searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 until March 2022. We analyzed data on patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

RESULTS: Twenty-nine publications with 119 patients (females n=75, age range 20-93 years, AChR Ab positive n= 65, MuSK Ab positive n= 5, seronegative n=14, unknown n=35) were included. Eighty-three (70%) were hospitalized, more than half with MG exacerbation. There was no significant difference in disease duration or control of MG symptoms at baseline between hospitalized and non-hospitalized. Hospitalization was associated with higher dose of daily prednisone, but a comparable proportion of patients were on steroid-sparing agents. Among hospitalized patients, 40% were intubated uncorrelated with MG baseline control. Unfavorable outcomes were not always associated with MG exacerbation. Amongst those discharged, 75% received intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX) for MG exacerbation as compared to 67% with a fatal outcome didn't receive either.

CONCLUSION: Preexisting MG does not appear to be associated with severe COVID-19 outcomes. A higher dose of prednisone prior to COVID-19 infection is associated with increased risk of hospitalization but MG control at baseline did not determine worse outcome. IVIG/PLEX appear safe in patients with COVID-19 experiencing MG exacerbation.

Introduction

Myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, commonly requires immunosuppressive treatment putting patients at a potentially increased risk for infections.[1] Patients with MG are susceptible to respiratory infections such as COVID-19 due to their neuromuscular weakness.[2] These patients can develop respiratory insufficiency, which could lead to a perilous clinical course from COVID-19 pneumonia. Furthermore, COVID-19 can itself precipitate MG exacerbation since infections are known to be common triggers.[3] Antibiotics used to treat secondary pneumonia and possibly medications such as hydroxychloroquine, used early in the pandemic, can potentially worsen MG.[4] Given the uncertainties surrounding COVID-19, especially at the beginning of the pandemic and the persistent emergence of new variants and treatment protocols, treating COVID-19 patients with known MG has remained an ongoing challenge.[5] The fluctuating course of MG and the wide variations seen between MG patients further complicated this challenge.

Over the course of the pandemic, several case reports of COVID-19 in patients with known MG have been described. These have suggested highly variable clinical courses with some attributing pre-existing myasthenia to worse COVID-19 outcomes, whereas others speculate that COVID-19 itself was responsible for the eventual outcome. Yet systematic evidence on the factors such as the role of steroids taken for MG control, which could alter COVID-19 outcomes in this population, remains scarce. This study thus attempts to aggregate information presented across all such published cases in order to investigate predictors of outcomes in MG patients with concomitant COVID-19 infection.

We performed a systematic review of the relevant literature with key aims to assess two specific outcomes of COVID-19 in patients with pre-existing MG. The first outcome is hospitalization, for which we compared clinical characteristics of patients who were hospitalized with those who did not require hospitalization. Second, among hospitalized patients, we identified factors associated with severe outcomes requiring subsequent invasive ventilation and/or mortality.

Methods

Following the recommendations of Preferred Reporting Items for Systematic Review and Meta-Analysis checklist (PRISMA)[6] for conducting systematic reviews, we searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 infection until March 2022 with keywords "COVID-19" and "myasthenia gravis." For our analysis, we excluded registries or studies with little detail of individual patients which were insufficient to answer our

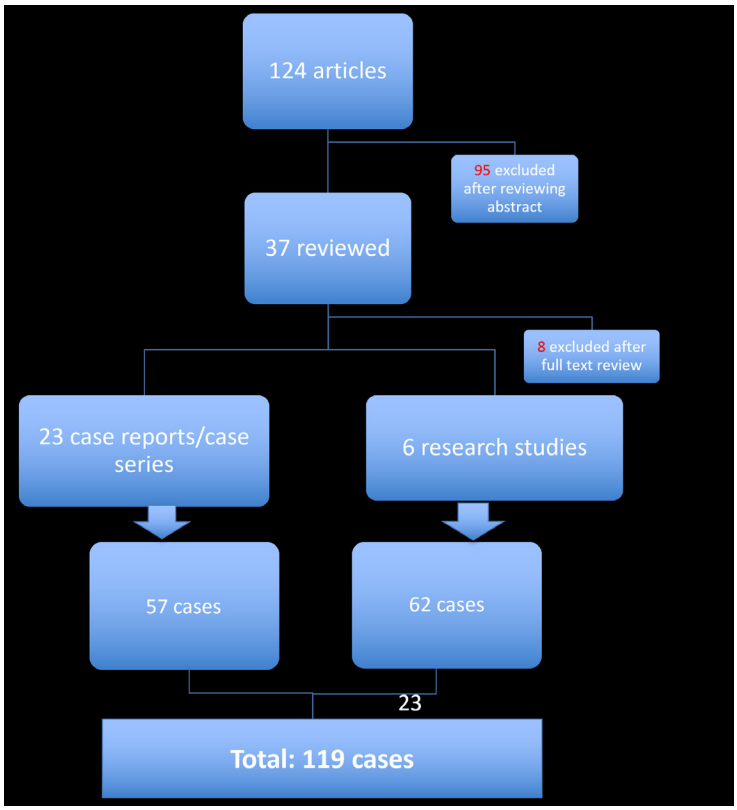


Figure 1: Flowchart showing search process, outcomes and included studies conducted in accordance with PRISMA guidelines for systematic reviews[6]

research question. Additionally, exclusion of those studies helped us to ensure we were not including duplicate cases. We systematically collated a dataset including patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

We used two widely accepted MG outcome measures, Myasthenia Gravis Foundation of America (MGFA) class and Myasthenia Gravis Activities of Daily Living (MGADL) scores, to define MG control.[7] Patients with MGFA classes I, IIA and IIB or MGADL score of <6[8,9] were classified as MG controlled at baseline or having milder disease. Further, to determine favorable vs unfavorable outcome amongst hospitalized patients, we defined favorable outcome as patients who were discharged to home or facility. Death and continued hospitalization with intubation were considered unfavorable outcomes. When information was inadequate or unavailable for certain parameters for individual cases, those were excluded from the denominator for analysis.
Statistical analyses were performed with the following details. For continuous variables of normal distribution, the statistic reported is mean ± standard deviation, while the median is reported for variables with skewed distributions. For categorical variables frequencies and percentages are reported. Continuous variables were compared by Student's t-test and categorical variables were compared by two sample Z-test of proportions. A p-value < 0.05 was considered statistically significant.

Results

We found a total 124 articles based on keyword search and after reviewing all abstracts, following the criteria described in methods, 37 were reviewed in detail (Figure 1). Eight of these were further excluded because they were aggregated analyses of registries or studies with little details of individual patients. Finally, we were able to include 23 publications with case reports or case series, and 6 studies (observational or cross-sectional) describing 62 patients cumulatively with individual details. The final dataset comprised of 119 patients (Figure 1) whom we analyzed assessing their outcome and potential predictors for Covid-19 outcomes.

Out of 119 patients, the majority (N=83 (70%) was hospitalized (median age of 56 years, 54% females) (Table 1). Non-hospitalized patients were more commonly females (83%, p <0.05) and younger (median age 43.5 years, p <0.05) and more frequently noted to have a history of thymectomy (94%. p <0.05). Patients who were hospitalized more likely had comorbidities (72%, p<0.05). Although a comparable proportion of patients were on

Table 1: Comparison between hospitalized and non-hospitalized patients

Demographic and clinical characteristics	Non hospitalized N=36	Hospitalized N=83	p value
Female	30/36 (83)	45/83(54)	0.003
Mean Age (Range) (yrs)	48.1 (21-86) (Median 43.5) (N=36)	56.4 (25-93) (Median 56) (N=68)	0.013
Mean Duration of MG (Range) (yrs)	8.7 (0.75-35) (Median 6) (N=24)	6.7 (0.25-25) Median (4.2) (N=64)	0.126
AChR Ab positive	17/23 (74)	48/61 (79)	0.638
MuSK Ab positive	0/23 (0)	5/61(8)	0.156
Double seronegative	6/23 (26)	8/61 (13)	0.156
History of thymoma	9/16 (56)	6/24 (25)	0.045
History of thymectomy	15/16 (94)	25/61 (41)	0.001
Comorbidities	11/36 (31)	48/67 (72)	<0.001
On oral steroids at baseline	21/36 (58)	59/83 (71)	0.174
On high dose prednisone or equivalent (>20mg/day)	5/24 (21)	32/60 (53)	**0.007**
On steroid sparing agent	18/36 (50)	47/83(57)	0.503
MG controlled at baseline	28/35 (80)	60/69 (87)	0.352
Evidence of MG exacerbation	1/36 (3)	45/80 (56)	<**0.001**
Received antibiotic or antiviral	18/36 (50)	64/81 (79)	**0.0015**
Received HCQ for COVID?	0/37 (0)	12/82 (15)	**0.014**
Received tocilizumab for COVID?	0/37 (0)	5/82 (6)	0.126
Intubation	0/37 (0)	38/83 (46)	<**0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

steroid-sparing agents for both groups, hospitalization was associated with a higher dose (prednisone>20mg/day or equivalent) of daily oral steroids (53% vs 21%, $p<0.05$). Unlike age, disease duration of myasthenia was not different between hospitalized and non-hospitalized patients (Figure 2).

Among hospitalized patients, males (86%) and elderly (median age 68yrs, $p<0.05$) were more likely to have unfavorable outcomes and prior disease duration was unrelated (Table 2, Figure 3). Usage of antibiotics or antivirals was not significantly different amongst hospitalized patients with favorable or unfavorable outcomes. Interestingly, 18/30 (60%) patients who received azithromycin and 4/5 (80%) patients who received fluoroquinolones showed evidence of MG exacerbation. However, only 4/12 patients who took HCQ reported MG exacerbation.

Forty six percent of hospitalized patients required intubation, but this was not associated with MG baseline control (68% vs 76%, $p > 0.05$). More than half (56%) of the hospitalized patients showed evidence of MG exacerbation. Unfavorable outcome was not always associated with MG exacerbation (62% vs 77%, $p<0.05$). Amongst 38 hospitalized patients with MG exacerbation whose outcomes could be determined, 28 had a favorable outcome with 21 (75%) of them having received either IVIG or PLEX. On the contrary, only four out of 10 with unfavorable outcome received either therapy (40%). Among the remaining six with unfavorable outcome who received neither, death was confirmed for 4 patients.

Discussion

MG patients who contract COVID-19 are expectedly at increased risk of hospitalization and likely to have longer duration of hospital stay, which recent studies analyzing data from registries have confirmed.[10-12] However, determinants for risk of hospitalization and poor outcome in hospitalized MG patients were not well-established. The limited studies on MG patients with COVID-19 have documented diverse clinical course with only few potential predictors of outcome.[13,14] To address this gap, we compared hospitalized and non-hospitalized patients and further compared between hospitalized patients with or without favorable outcomes. There was no significant difference in MG disease duration (Figure 2) and antibody positivity status between hospitalized and non-hospitalized groups. We found male and elder myasthenics are more likely to be hospitalized and more likely to have poor outcome when hospitalized. Studies worldwide similarly have shown elderly[15] and men are likely to have worse COVID-19 outcomes[16-18] including patients with neuromuscular disorders.[19] On the contrary, myasthenia tends to have a more severe course in females.[20] Thus, COVID-19 appears to be the dominant factor in shaping outcomes in patients with concomitant MG and COVID infection. Unsurprisingly, comorbidities found previously to be significant risk factors for severe COVID-19 infection[21,22] were more common amongst hospitalized MG patients in our dataset. Additionally, MG control at baseline was unrelated to hospitalized patients being intubated. Unfavorable outcome in hospitalized patients was not always associated with MG exacerbation. Our analysis thus suggests pre-existing MG did not appear to be a major factor in worsening outcome from COVID-19 infection.

We found high dose of oral steroids to be associated with increased risk for hospitalization. Baseline long-term corticosteroid treatment, especially in high dose, has been noted to predict severe course of COVID-19 in a study on MG patients.[23] This highlights why reducing or discontinuing steroids without losing MG control should be the therapeutic goal when managing MG. Interestingly high dose of prednisone at baseline did not predict poor outcome amongst hospitalized patients in our analysis. Furthermore, administration of extra steroids during hospitalization also did not seem to affect the outcome (Table 2). The lack of such association could possibly be explained by the potential beneficial role of steroids in severe COVID-19 infection[24] but not in mild COVID.[25] The majority of non-hospitalized patients had h/o thymectomy and 85% patients with thymectomy in our cohort had MG controlled. While a protective role of thymus gland has been suggested in viral infection like COVID-19,[26] thymectomy is known to render improved clinical outcome in MG[27] and perhaps accounted for a lesser risk of a severe clinical course. No significant association of poor outcome was noted with non-steroid sparing agents, as observed in COVID-19 and other autoimmune conditions.[28]

Both IVIG and PLEX are effective treatments for myasthenic crisis. The beneficial role of therapeutic plasma exchange[29] and IVIG[30] also has been observed in severe COVID-19 infection, although debate continues with concern for increased thromboembolic events particularly in relation to IVIG.[31,32] In the cases we reviewed, most hospitalized patients with COVID-19 appeared to have benefitted from IVIG/PLEX for MG exacerbation. These regimens appear safe in COVID-19 patients who experience MG exacerbation.

One of the major limitations of the study is reporting bias since our review is primarily based on published case reports and case series. Given the publishing bias in case reports and high incidence of hospitalization in our cohort, the findings of the study perhaps can be interpreted as characterizing severe COVID-19 infection among MG patients. Additionally, marked heterogeneity of study population due to variation in geographical origin, practiced standard of care, as well as often limited information due to non-uniform reporting could not be adjusted for. Nevertheless, several of our study findings,

including more favorable COVID-19 outcomes in females and increased risk for hospitalization due to comorbidities, lend face validity to our dataset. Additional studies may utilize data from MG cohorts from individual institutions or databases. None of the studies we reviewed reported whether patients were vaccinated. Given these studies were published prior to March 2022, it is highly plausible that most cases occurred before vaccines for COVID-19 were widely available around the world. While it is true that vaccines could alter the course of COVID-19 in MG patients and having that information would be helpful, studies like ours provide clinical implications of managing MG should any future pathogens result in epidemics for whom vaccines may not become immediately available.

Conclusion

Pre-existing myasthenia gravis is potentially a risk factor for worse outcomes in COVID-19. Yet, given MG itself is a disease with a highly variable course, it is important to establish the specific factors among MG patients that could alter COVID-19 outcomes. We aggregated data combining a large number of published cases of MG patients diagnosed with COVID-19 and found that pre-existing MG itself does not predict a worse COVID-19 outcome. Rather, the factors typically associated with worse COVID-19 outcomes, irrespective of MG diagnosis, also led to poorer outcomes in MG patients who contracted COVID-19.

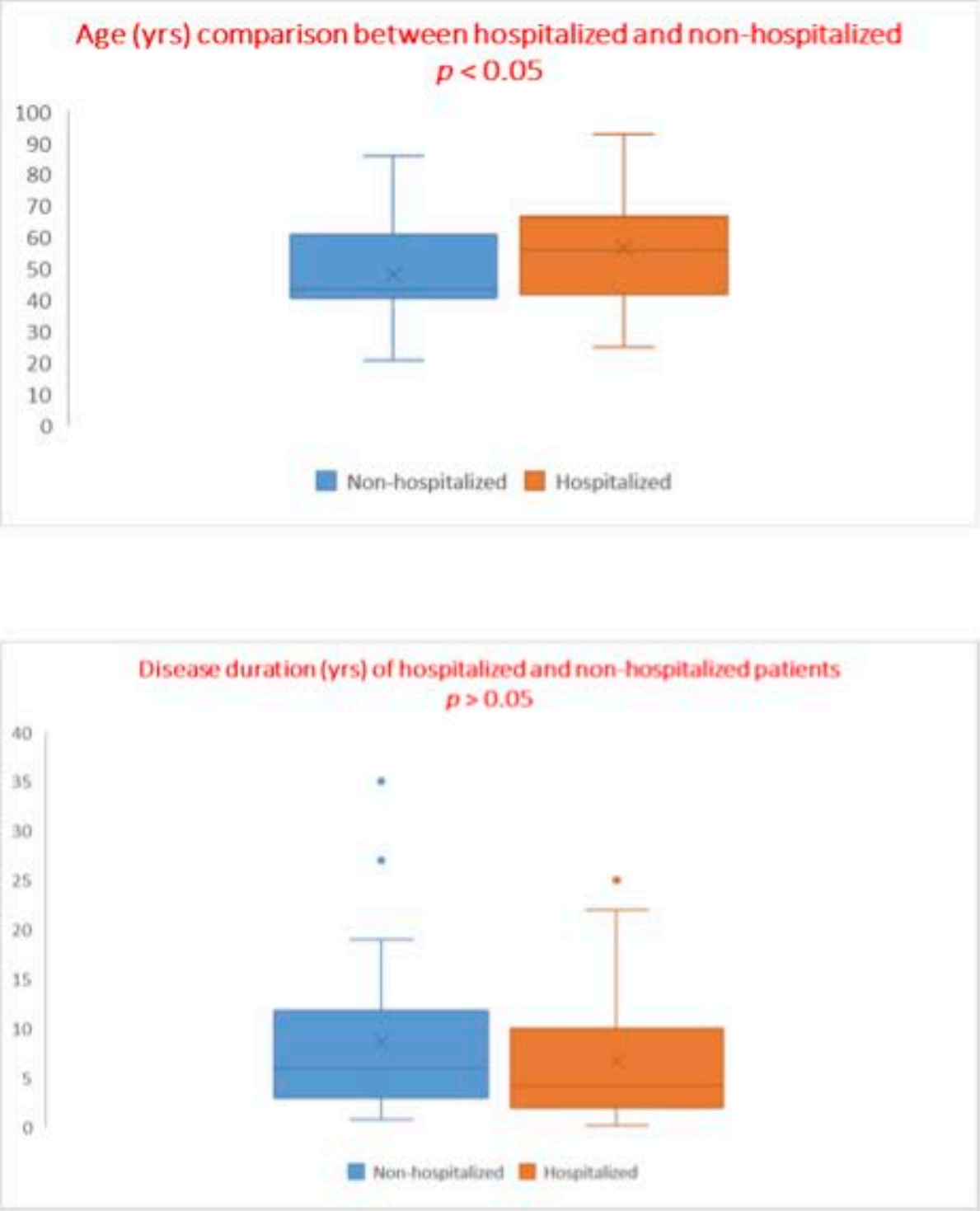
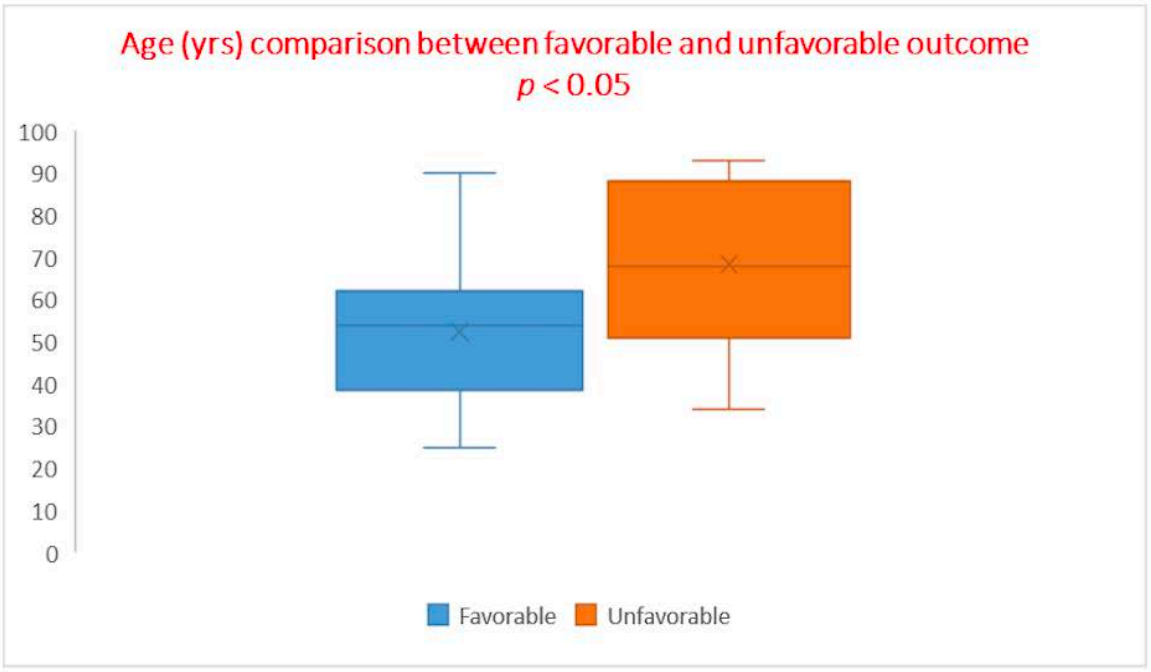


Figure 2: Differences in hospitalized vs non-hospitalized patients based on age (top) and disease duration (bottom)



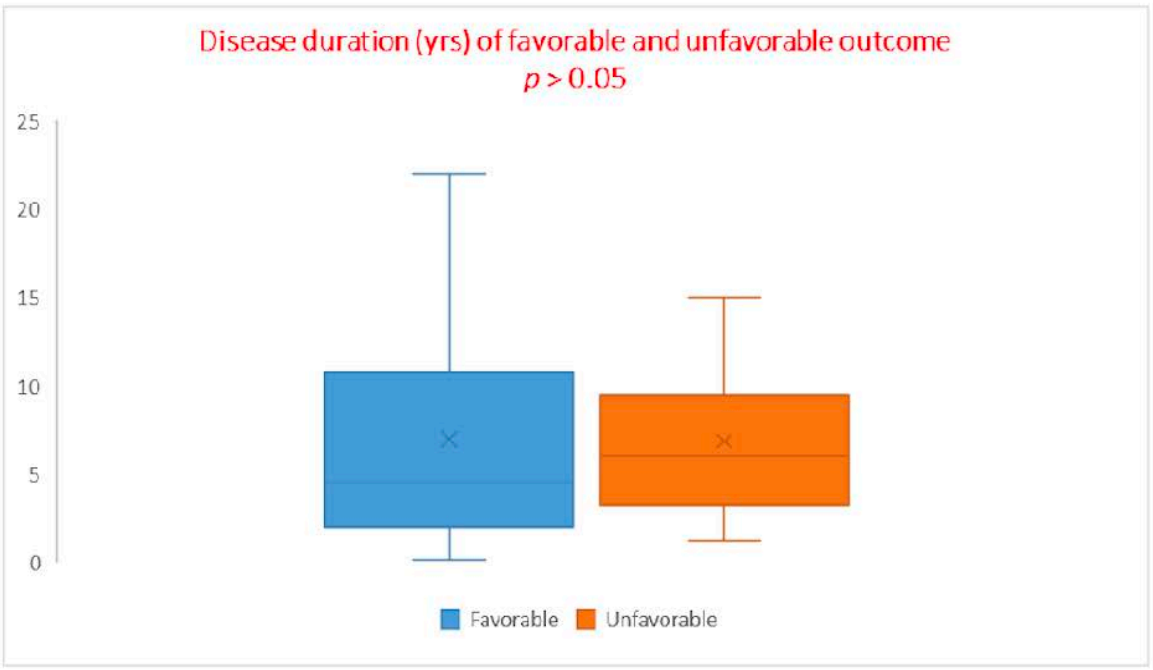


Figure 3: Differences in hospitalized patients' favorable vs un-favorable outcomes based on age (top) and disease duration (bottom)

TABLE 2 Comparison between favorable and non-favorable outcome among hospitalized patients

Demographics and clinical characteristics	Favorable outcome N=49	Non favorable outcome N=17	*p* value
Female	20/36 (56)	1/7 (14)	0.046
Mean Age (Range) (yrs)	52.4 (25-90) (Median=54) N=40	68.5 (34-93) (Median=68) N=16	**0.007**
Duration of MG (Range) (yrs)	6.9 (0.16-22) (Median=4.5) N=44	6.8 (1.2-15) (Median=6) N=12	0.493
AChR Ab positive	31/41 (76)	11/12 (92)	0.226
MuSK Ab positive	3/41 (7)	1/12 (8)	0.904
Double seronegative	7/41 (17)	0/12 (0)	0.124
History of thymoma	3/15 (20)	1/4 (25)	0.825
History of thymectomy	16/38 (42)	2/9 (22)	0.271
Comorbidities	22/34 (65)	13/16 (81)	0.234
On oral steroids at baseline	33/48 (69)	13/17 (77)	0.548
On high dose prednisone or equivalent (>20mg/day)	21/37 (57)	9/17 (53)	0.795
On steroid sparing agent	25/48 (52)	9/17 (53)	0.952
MG controlled as baseline	36/41 (88)	11/14 (79)	0.395
Evidence of MG exacerbation	28/45 (62)	10/13 (77)	0.327
Received antibiotic or antiviral	34/48 (71)	15/16 (94)	0.061
Received tocilizumab/HCQ	9/48 (19)	2/16 (13)	0.569
Extra steroids administered during hospitalization	25/40 (63)	6/14 (43)	0.201
Received IVIG or PLEX For MG exacerbation	21/28 (75)	4/10 (40)	**0.045**
Intubation	19/48 (40)	15/17 (88)	**0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

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